Amendments to the Drawings:

The sheet of drawings attached in the Appendix includes changes to Figs. 1-36. These sheets replace the original sheets. The drawings have been changed as follows: the figure legened (the text following the figure number) has been deleted in each of the 36 figures. The following is an example:

Figure 1~~: Effects of N,N' (1,2 phenylene) dimaleimide (oPDM), protamine sulfate (PS) and ovotransferrin (OT) alone and in combinations (oPDM+PS and oPDM+OT) on biofilm formation in *E. coli* P18~~

REMARKS

Applicants respectfully request entry of the Amendment and reconsideration of the claims. Claims 16-34 have been withdrawn. Claims 8 and 9 have been amended in view of the restriction requirement. No new matter has been added. Claims 1-15 and 35 will be pending upon entry of this amendment. Applicants respectfully request reconsideration of the claims and withdrawal of the pending claim objection and rejections under 35 U.S.C. § 112, first paragraph and 35 U.S.C. § 103(a).

Restriction Requirement

Applicant acknowledges the restriction requirements of January 13, 2005 and March 11, 2005, which are reflected in the current claim listing. Claims 1 to 15 and 35 are currently under examination.

Priority

The reference to related applications at page 1 of the specification has been updated. The current application claims priority to U.S. provisional application no. 60/588,132, filed on April 1, 2004.

Drawings

The Examiner objected to the drawings for containing figure legends. The drawings have been amended to delete the figure legends.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejects claims 1-6, 8-10, 15 and 35 under 35 U.S.C. § 112, first paragraph, for an alleged lack of enablement. The Examiner asserts that while enabling for a bacterial inhibiting composition comprising maleimides such as N-phenylmaleimides, the specification does not reasonably provide enablement for a bacterial inhibition composition comprising thiol-specific reagents. Applicant respectfully traverses.

To meet the enablement requirement of 35 U.S.C. §112, first paragraph, a specification must contain a sufficient description to enable one skilled in the art to make and use the claimed invention (*See, e.g., Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1253 (Fed. Cir. 2004); MPEP §2164.01). A specification does not need to explicitly disclose every detail, and may omit what is well known in the art (*In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991); MPEP 2164.01). To make and use an invention may require experimentation even if the specification is enabling (*In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988); *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984); MPEP 2164.01). The experimentation must not be unduly extensive (*Id.*), however, costly and timely experimentation alone does not constitute undue experimentation. (*U.S. v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988)).

Disclosure in the Specification. Applicants respectfully assert that the specification provides an enabling disclosure. Thiol-specific reagents were well known at the time of filing (see submitted references). Furthermore, the instant specification provides numerous examples of thiol-specific reagents, including maleimide compounds and non-maleimide compounds (*see*, e.g., page 14, paragraph [0075]) suitable for making and using the invention. The instant specification, in multiple embodiments, further teaches exemplary concentration ranges (at page 14, paragraph [0076]) for the thiol-specific reagents, suitable solvents (at page 16, paragraph [0082]), and methods for preparing the claimed compositions. Chemical structures, chemical properties, and methods of preparation of thiol-specific reagents were well known at the time of filing. Accordingly, Applicants respectfully assert that the specification provides guidance to make and use the claimed compositions.

Succinimides. In establishing a *prima facie* case of nonenablement, the Examiner has the burden of setting forth a reasonable explanation of why the claimed scope is not enabled by the specification. *In re Wright*, 999 F.2d 1557, 1561-1562 (Fed. Cir. 1993). The Examiner asserts that the prior art does not provide evidence that all thiol-specific reagents exhibit antimicrobial activity (Office Action at page 8). The Examiner cites Zentz et al. (2002) and Filho et al. (1994) to demonstrate that succinimides showed no antibacterial activity. Applicants respectfully assert that succinimides are not thiol-reactive compounds.

At the time of filing, it was well known that succinimides were not thiol-reactive compounds and, thus, are not within the scope of the instant claims. Succinimide compounds are

not considered "thiol-specific reagents"; whereas, maleimides and other non-succinimide compounds such as those set out in paragraph [0075] were well known "thiol-specific reagents". In fact, neither Zentz et al. nor Filho et al. teach or suggest that succinimides are thiol-reactive compounds or that all N-substituted imides having bactericidal properties are also thiol-reactive compounds.

Maleimides and succinimides are structurally distinct with the imido ring of the former having a double bond. As result of this structural difference, the chemical specificities of maleimides and succinimides are distinct. Maleimides preferentially oxidize thiol groups (*See e.g.*, Becker et al., 2003, *Journal of Investigative Dermatology*, 120: 233-238 (abstract), which characterizes N-hydroxymaleimide and N-ethylmaleimide as thiol-reactive reagents and sulfosuccinimdyl acetate as an amino-reactive agent). Maleimides react with cysteines but not tyrosines, histidines, or methionines (*See, e.g.*, discussion of maleimides at http://www.piercenet.com/Proteomics/browse.cfm?fldID=CE4D6C5C-5946-4814-9904-C46E01232683, copy attached). In contrast, succinimides preferentially oxidize amino groups (Becker et al., 2003) and react with methionines (Becker et al., 2003; Kikuchi et al., 2000, *Am. J. Respir. Cell Mol. Biol.*, 23: 364-370, at p. 365, 2nd col., 2nd paragraph) and in some cases, tyrosines and histidines, depending on the particular succinimide compound (Lishcwe and Sung, 1977, *J. Biol. Chem.*, 252: 4976-4980, at p. 4979, 2nd col., 3rd paragraph). As such, succinimides are structurally distinct from maleimides and are not thiol-specific.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. § 103(a)

The Examiner rejects the claims under 35 U.S.C. § 103(a) for alleged obviousness. Specifically, the Examiner rejects a) claims 1-3, 5-8, and 10-12 over U.S. Pat. No. 5,688,516 (Raad et al.) in view of Filho et al. (cited in the IDS filed August 27, 2004); b) claims 1, 5-10, and 35 over U.S. Pat. No. 4,845,256 (Mebes et al.) in view of Filho et al.; c) claims 1-2, 4-9, and 13-14 over U.S. Pat. Pub. No. 2002/0133169 (Berry) over Filho et al.; and d) claims 1-15 over U.S. Pat. No. 5,688,516 (Raad et al.) in view of Filho et al. and further in view of U.S. Pat. No. 6,528,107 (Chinn et al.). Applicant assumes that the Examiner made a typographical error

regarding the date of publication of Filho et al. and is referring to Cechinel Filho et al., 1994, *Farmaco*, 49: 675-677. Applicant respectfully traverses.

Prima Facie Obviousness. To establish a *prima facie* case of obviousness, three criteria must be met--a suggestion or motivation to combine references, a reasonable expectation of success, and the prior art reference teaches or suggests all the claim limitations. MPEP §2143; *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Applicant respectfully asserts that there is no reasonable expectation of success nor do the prior art references teach or suggest all of the claim limitations. Applicant respectfully asserts that the Examiner has not met the criteria for establishing obviousness under 35 U.S.C. §103(a).

In each of the four separate rejections under 35 U.S.C. §103(a) for alleged obviousness (as characterized by Applicant in the above as (a) - (d)), at least one of the cited art references fails to teach antibiofilm properties. Specifically, Mebes et al., Berry, and Filho et al. do not teach antibiofilm properties, but rather only teach antimicrobial properties. Biofilms can resist antimicrobial treatments, or to a much larger degree, than planktonic cells of individual microorganisms that comprise a biofilm. *See* Donlan, 2001, *Emerg. Infect. Dis.* 7: 277-281 (at p. 277, column 2; cited in the IDS filed August 27, 2004). In fact, biofilms are inherently "much less susceptible to antibiotics" and "can evade antimicrobial challenges by multiple mechanisms." *See* Costerton et al., 1999, *Science* 284: 1318-1322 (at p. 1319, column 2; cited in the IDS filed August 27, 2004). A demonstration of antimicrobial properties does not necessarily translate to antibiofilm properties. As such, the Examiner has not established a reasonable expectation of success in any of the four prior art combinations used to reject the claims under 35 U.S.C. §103(a).

Since Mebes et al., Berry, and Filho et al. do not teach or suggest antibiofilm properties, the rejections under 35 U.S.C. §103(a) for alleged obviousness over Mebes et al. or Berry in view of Filho et al. do not teach or suggest all of claim limitations. Claim 1 and all subsequent dependent claims are compositions for inhibiting bacterial biofilms. For the aforementioned reasons, a biofilm comprising a heterogeneous population of bacteria are not susceptible to antimicrobials in a manner like planktonic bacteria or a homogeneous population of bacteria. As such, Mebes et al. or Berry in combination with Filho et al. do not teach a composition with antibiofilm properties.

Applicants respectfully assert that the Examiner has not established a *prima facie* case of obviousness since there is not a reasonable expectation of success nor a teaching or suggestion of all the claimed limitations.

Unexpected Success. Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness. MPEP 716.02; In re Chupp, 816 F.2d 643, 646 (Fed. Cir. 1987).

> A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness...of the claims at issue. *In re Corkill*, 771 F.2d 1496, 1501 (Fed. Cir. 1995); MPEP 716.02(a)

Evidence of a greater than expected result may be shown by demonstrating an effect that is greater than the sum of each of the separate effects. *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989); MPEP 716.02(a).

Applicants respectfully assert that the claimed combinations produced unexpected results, although Applicant does not acquiesce to the assertion that the Examiner has established a case of *prima facie* obviousness. Compositions comprising a thiol-specific reagent and a cationic polypeptide, a thiol-specific reagent and an iron-sequestering glycoprotein, or a thiol-specific reagent and a quaternary ammonium compound have synergistic antibiofilm properties as compared to the antimicrobial properties of the individual components of the claimed compositions. Combining a thiol specific reagent with a cationic polypeptide yields an unexpected result of a composition having synergistic antibiofilm properties as compared to the antibiofilm properties of either thiol specfic reagents or cationic polypeptides alone. Examples 1, 2, 3, and 5 of the present application clearly demonstrate the synergistic effects of combining N'-(1,2-phenylene) dimaleimide (oPDM) or N-(1-pyrenyl) maleimide (PyrM) (thiol specific reagents) with protamine sulfate (PS, a cationic polypetide). The specification discloses the synergistic inhibitory effects of oPDM + PS and PyrM + PS with respect to biofilm formation by *Proteus mirabilis*, *Staphylococcus epidermis*, and *Klebsiella pneumonaie*. *See*, e.g., at page 26, paragraph [0110]. The specification also discloses the synergistic inhibitory effect of oPDM + PS and PyrM + PS with respect to biofilm formation by *Escherichia coli* and *Enterococcus faecalis*. *See also*, at page 26, paragraph [0114]. Figures 1-12 also graphically depict the aforementioned antibiofilm effect of OPDM or PyrM with protamine sufate). Thus, the compositions of the present invention possess superior antibiofilm properties as compared to prior art antimicrobial compositions.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a).

CONCLUSION

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-0903
(612) 332-5300

Date: Aug. 2, 2005 ~~July 28, 2005~~

Ronald A. Daignault
Reg. No. 25,968
RAD:BRD:mls

23552
PATENT TRADEMARK OFFICE

Figure 1: ~~Effects of N,N' (1,2 phenylene) dimaleimide (oPDM), protamine sulfate (PS) and ovotransferrin (OT) alone and in combinations (oPDM+PS and oPDM+OT) on biofilm formation in *E. coli* P18~~

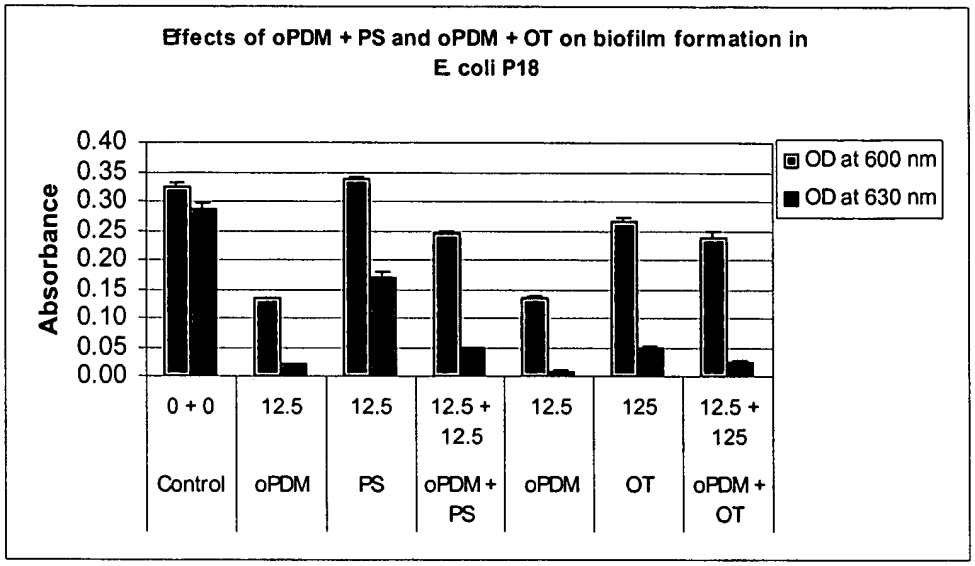

Figure 2: ~~Effects of N,N' (1,2 phenylene) dimaleimide (oPDM), protamine sulfate (PS) and ovotransferrin (OT) alone and in combinations (oPDM+PS and oPDM+OT) on biofilm formation in *Proteus mirabilis*~~

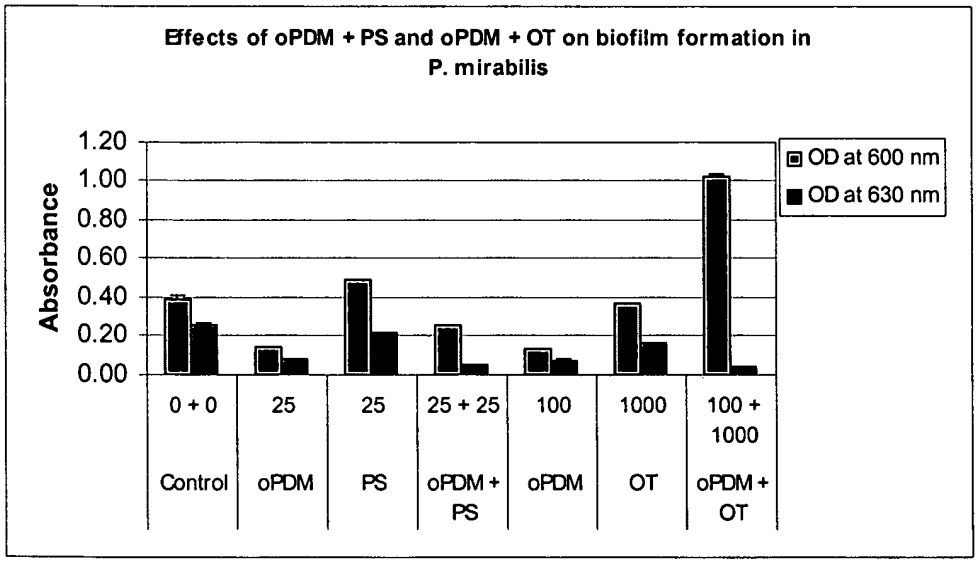

Figure 3: ~~Effects of N,N' (1,2 phenylene) dimaleimide (oPDM), protamine sulfate (PS) and ovotransferrin (OT) alone and in combinations (oPDM+PS and oPDM+OT) on biofilm formation in *Klebsiella pneumoniae*~~

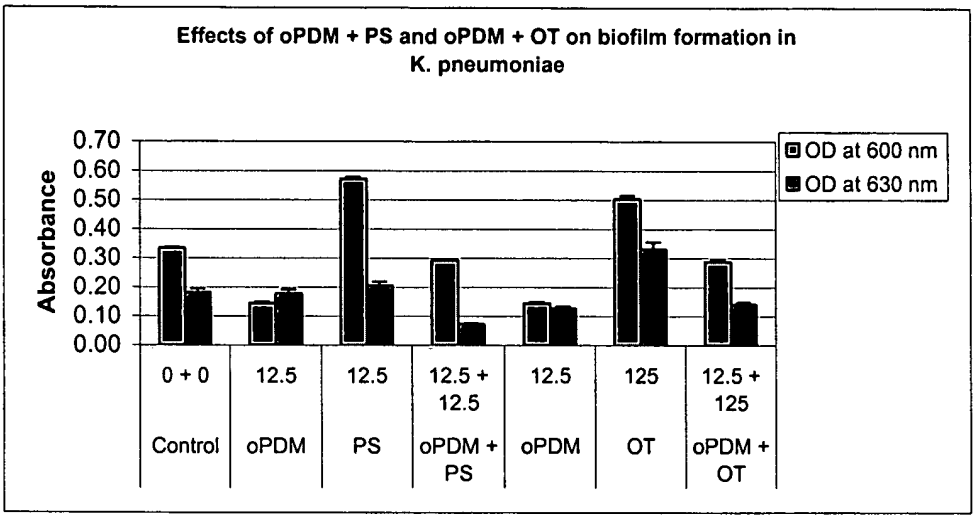

Figure 4: ~~Effects of N,N' (1,2 phenylene) dimaleimide (oPDM), protamine sulfate (PS) and ovotransferrin (OT) alone and in combinations (oPDM+PS and oPDM+OT) on biofilm formation in *Pseudomonas aeruginosa*~~

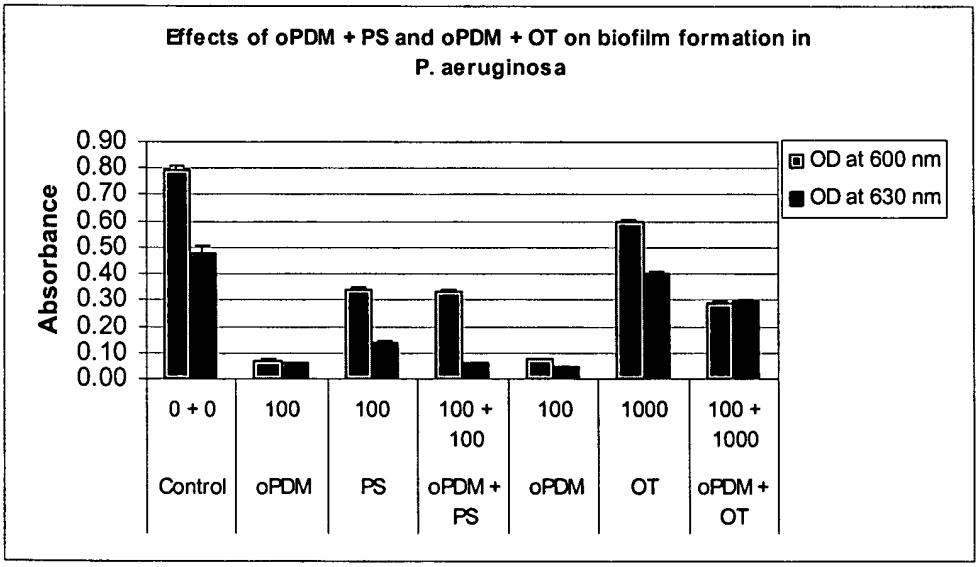

Figure 5: ~~Effects of N,N' (1,2 phenylene) dimaleimide (oPDM), protamine sulfate (PS) and ovotransferrin (OT) alone and in combinations (oPDM+PS and oPDM+OT) on biofilm formation in *Enterococcus faecalis*~~

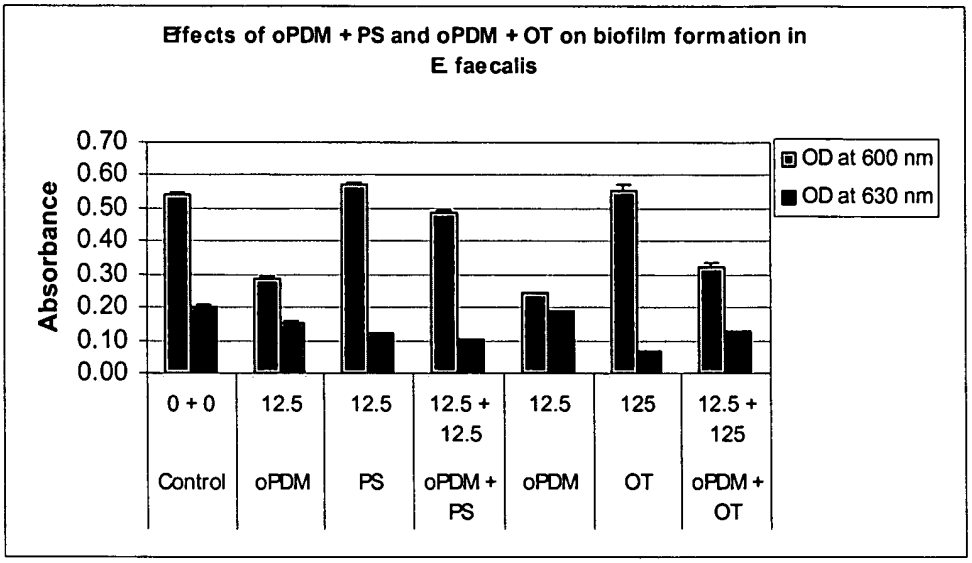

Figure 6: ~~Effects of N,N' (1,2 phenylene) dimaleimide (oPDM), protamine sulfate (PS) and ovotransferrin (OT) alone and in combinations (oPDM+PS and oPDM+OT) on biofilm formation in *Staph. Epidermidis*~~

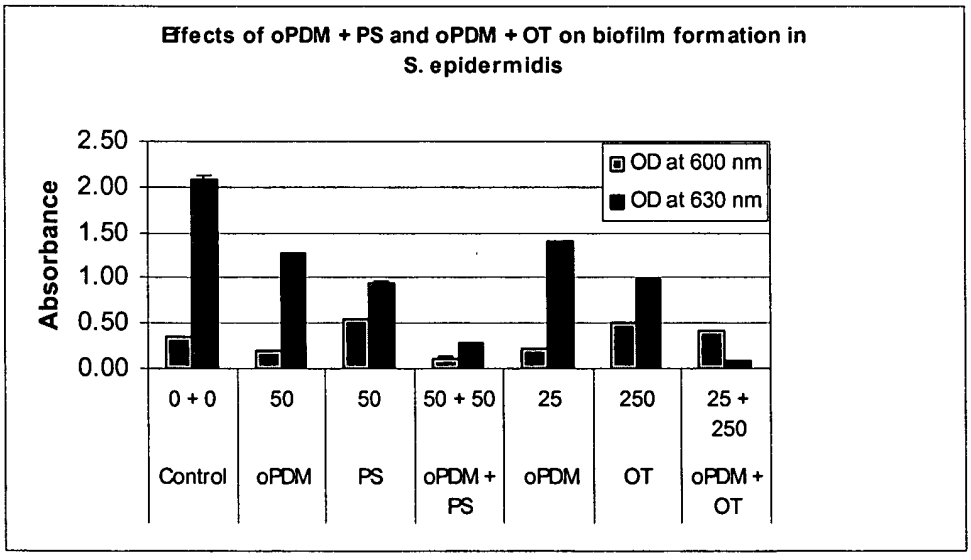

Figure 7: ~~Effects of N-(1-pyrenyl) maleimide (PyrM), protamine sulfate (PS) and ovotransferrin (OT) alone and in combinations (PyrM+PS and PyrM+OT) on biofilm formation in *E. coli* P18~~

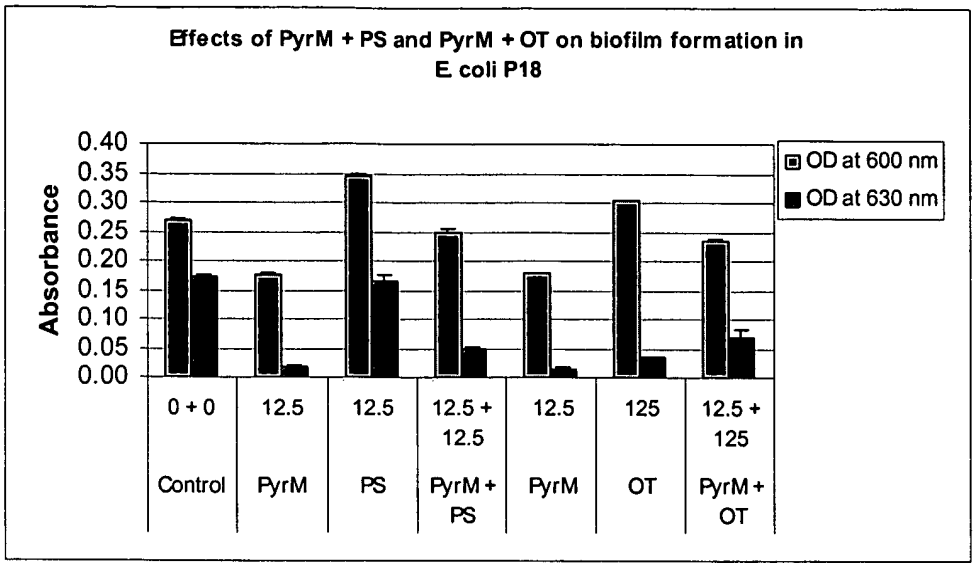

Figure 8: ~~Effects of N-(1-pyrenyl) maleimide (PyrM), protamine sulfate (PS) and ovotransferrin (OT) alone and in combinations (PyrM+PS and PyrM+OT) on biofilm formation in *Proteus mirabilis*~~

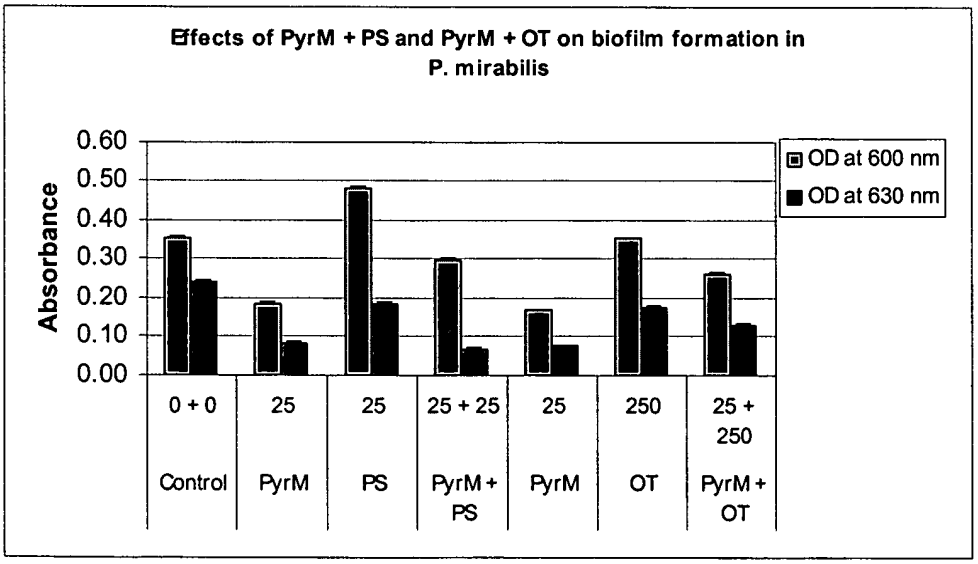

Figure 9: ~~Effects of N-(1-pyrenyl) maleimide (PyrM), protamine sulfate (PS) and ovotransferrin (OT) alone and in combinations (PyrM+PS and PyrM+OT) on biofilm formation in *Klebsiella pneumoniae*~~

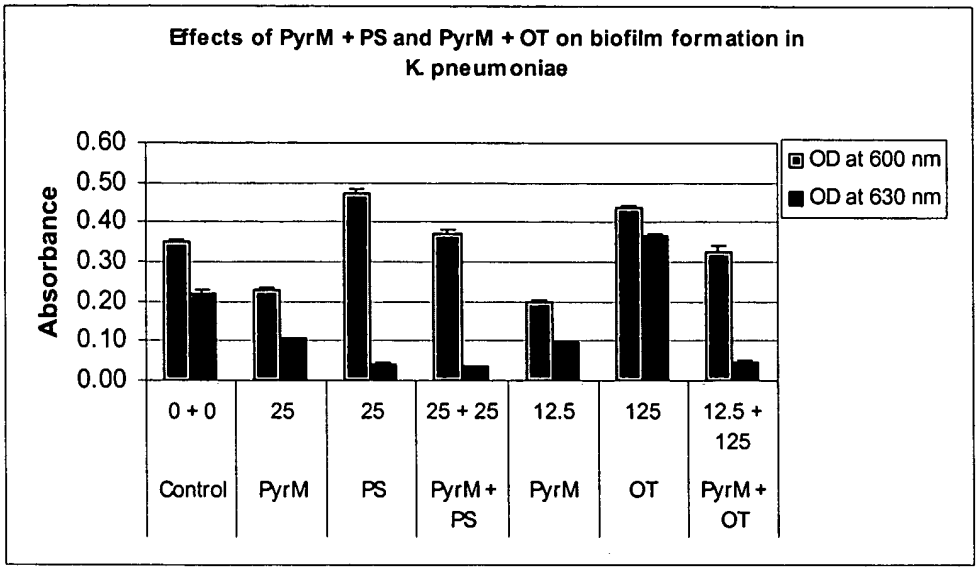

Figure 10: ~~Effects of N-(1-pyrenyl) maleimide (PyrM), protamine sulfate (PS) and ovotransferrin (OT) alone and in combinations (PyrM+PS and PyrM+OT) on biofilm formation in *Pseudomonas aeruginosa*~~

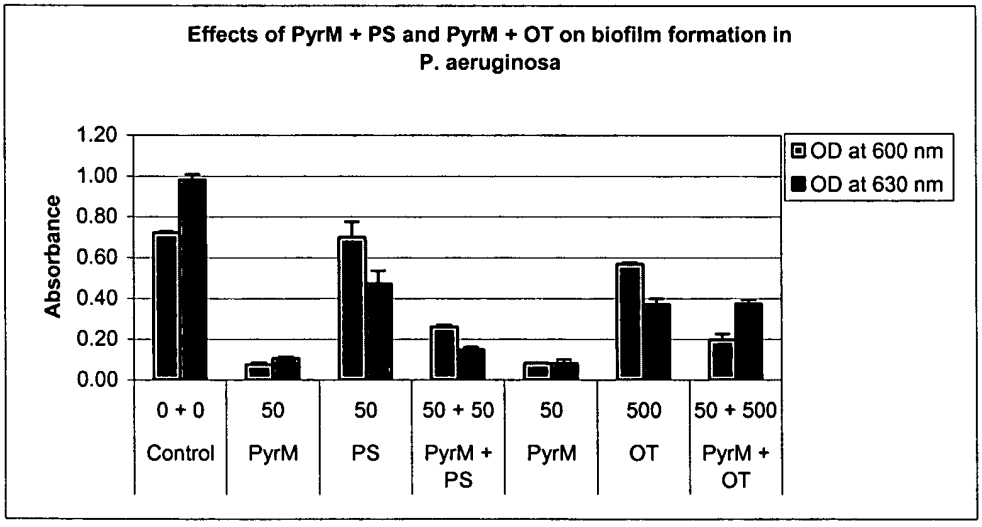

Figure 11: ~~Effects of N-(1-pyrenyl) maleimide (PyrM), protamine sulfate (PS) and ovotransferrin (OT) alone and in combinations (PyrM+PS and PyrM+OT) on biofilm formation in *Enterococcus faecalis*~~

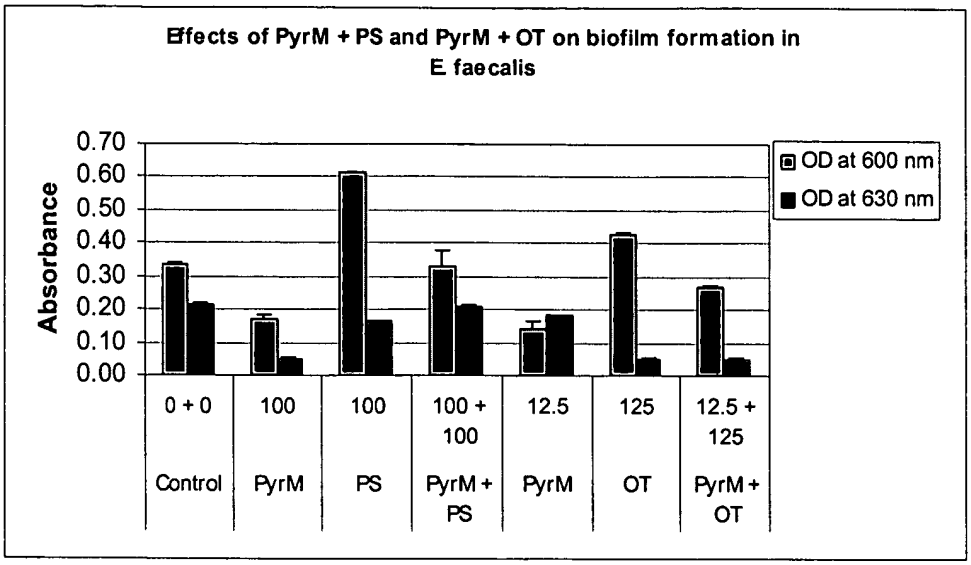

Figure 12: ~~Effects of N-(1-pyrenyl) maleimide (PyrM), protamine sulfate (PS) and ovotransferrin (OT) alone and in combinations (PyrM+PS and PyrM+OT) on biofilm formation in *Staph. Epidermidis*~~

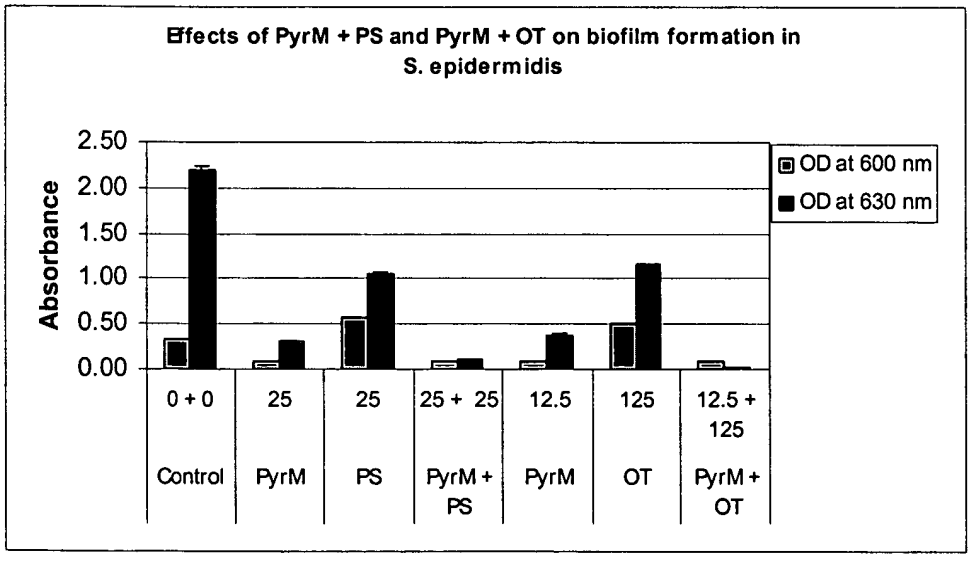

Figure 13: ~~Combined effects of N,N' (1,2 phenylene) dimaleimide and protamine sulfate on biofilm formation in *E. coli*.~~

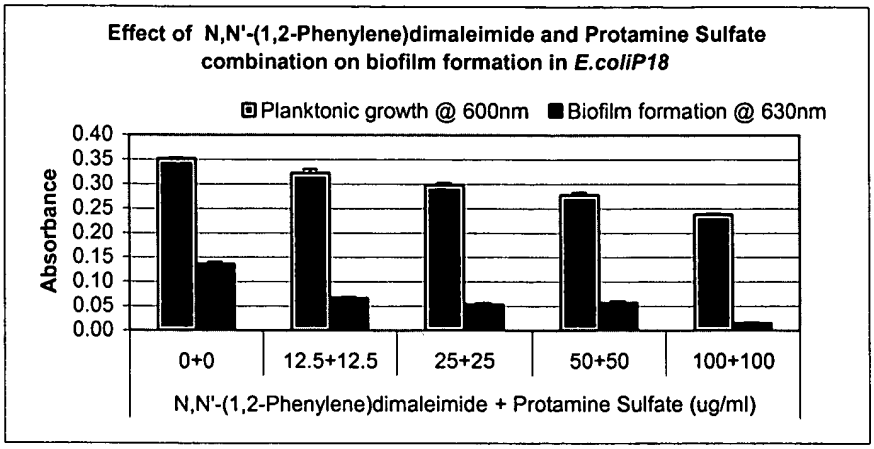

Figure 14: ~~Combined effects of N,N' (1,2 phenylene) dimaleimide and protamine sulfate on biofilm formation in *Proteus mirabilis*.~~

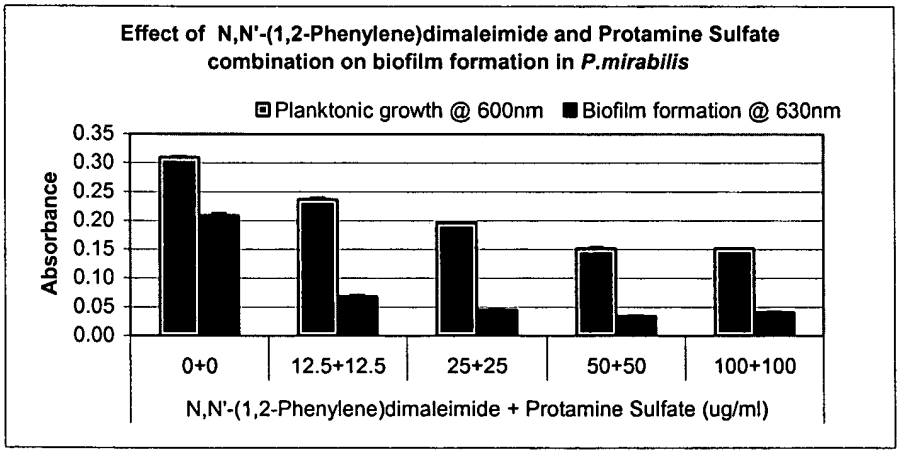

Figure 15~~: Combined effects of N,N' (1,2 phenylene) dimaleimide and protamine sulfate on biofilm formation in *Klebsiella pneumoniae*.~~

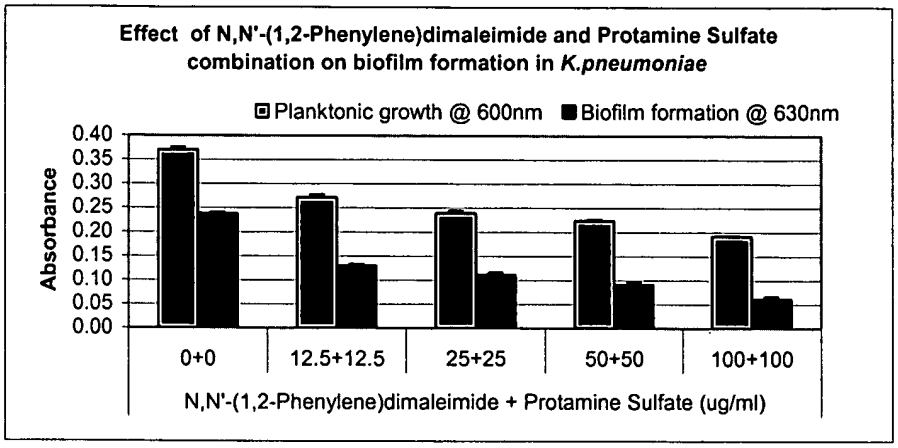

Figure 16~~: Combined effects of N,N' (1,2 phenylene) dimaleimide and protamine sulfate on biofilm formation in *P. aeruginosa*~~

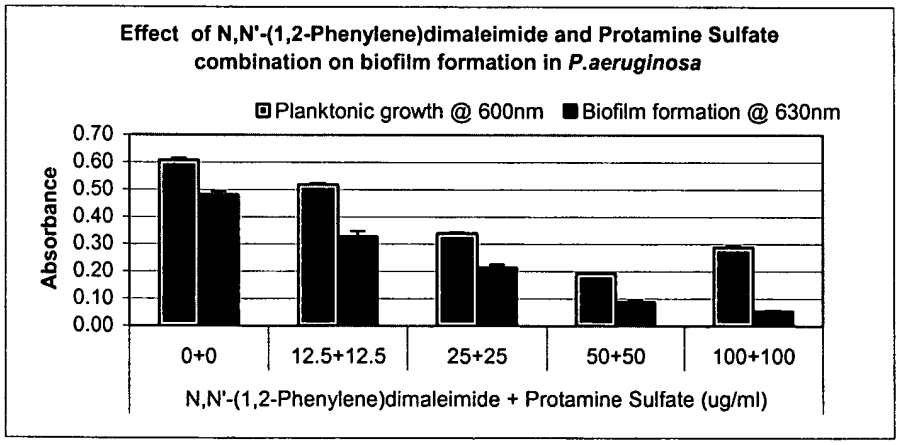

Figure 17~~: Combined effects of N,N' (1,2 phenylene) dimaleimide and protamine sulfate on biofilm formation in *Enterococcus faecalis*.~~

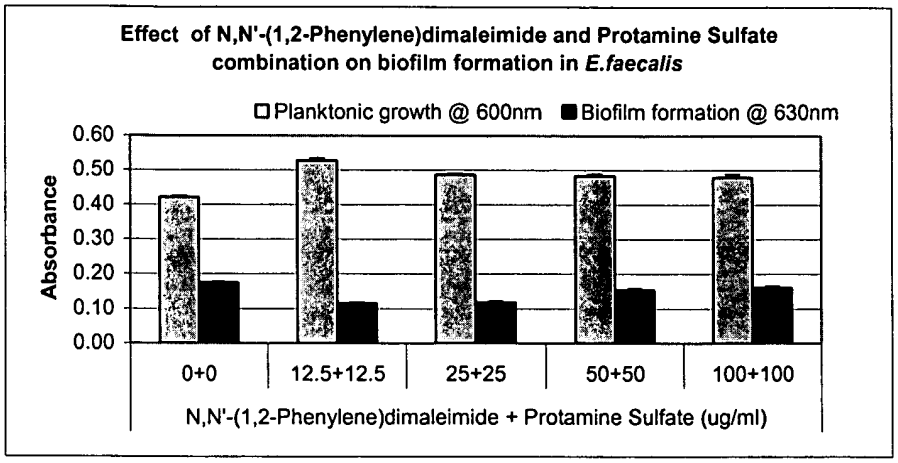

Figure 18~~: Combined effects of N,N' (1,2 phenylene) dimaleimide and protamine sulfate on biofilm formation in *Staph. epidermidis*.~~

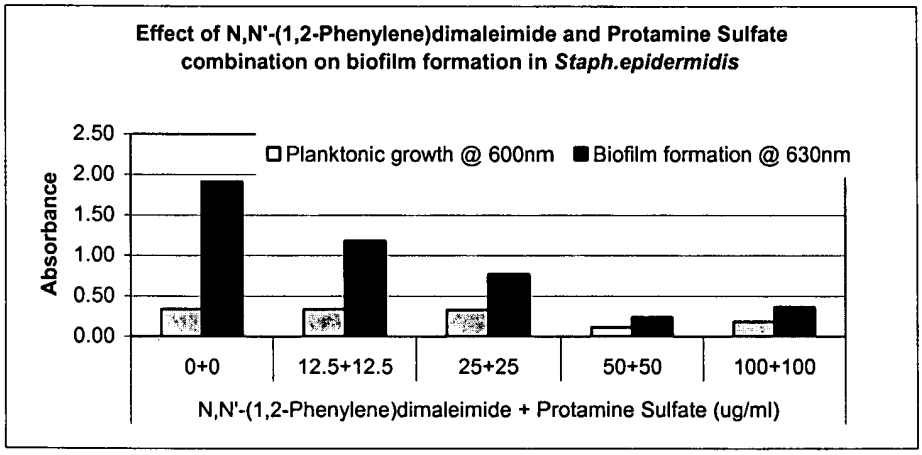

Figure 19~~: Combined effects of N,N' (1,2-phenylene) dimaleimide and ovotransferrin on biofilm formation in *E. coli* P18.~~

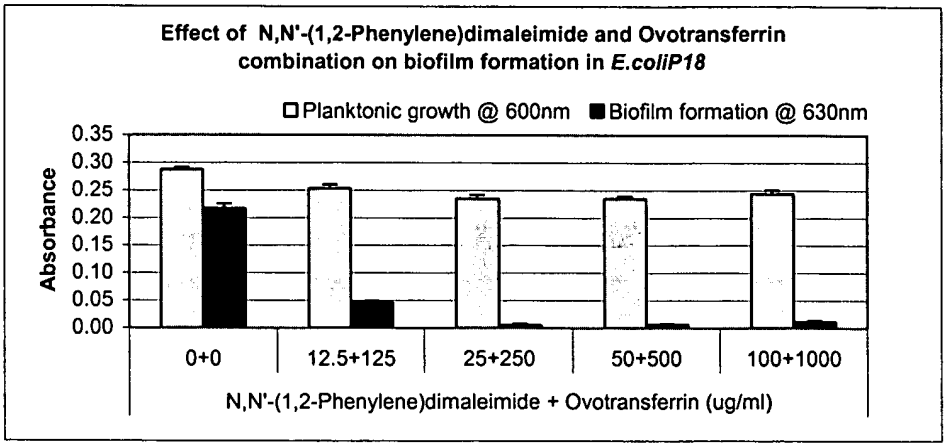

Figure 20~~: Combined effects of N,N' (1,2-phenylene) dimaleimide and ovotransferrin on biofilm formation in *Proteus mirabilis*.~~

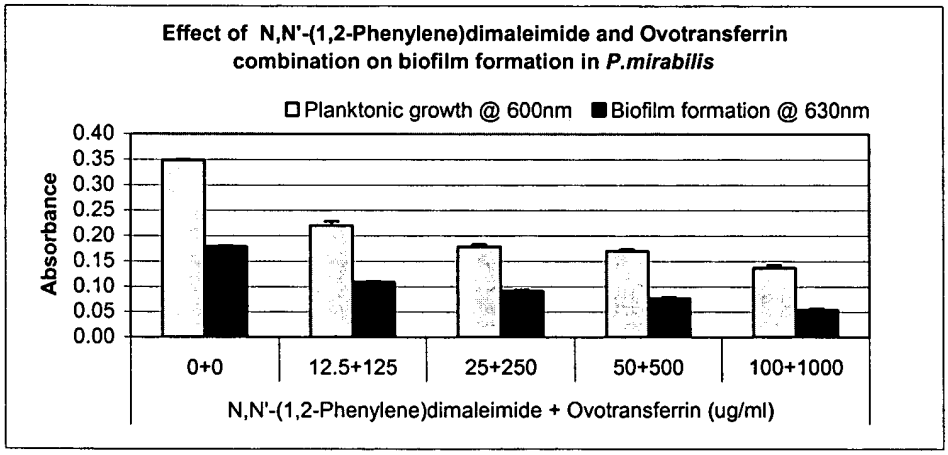

Figure 21: ~~Combined effects of N,N'-(1,2-phenylene) dimaleimide and ovotransferrin on biofilm formation in *Klebsiella pneumoniae*.~~

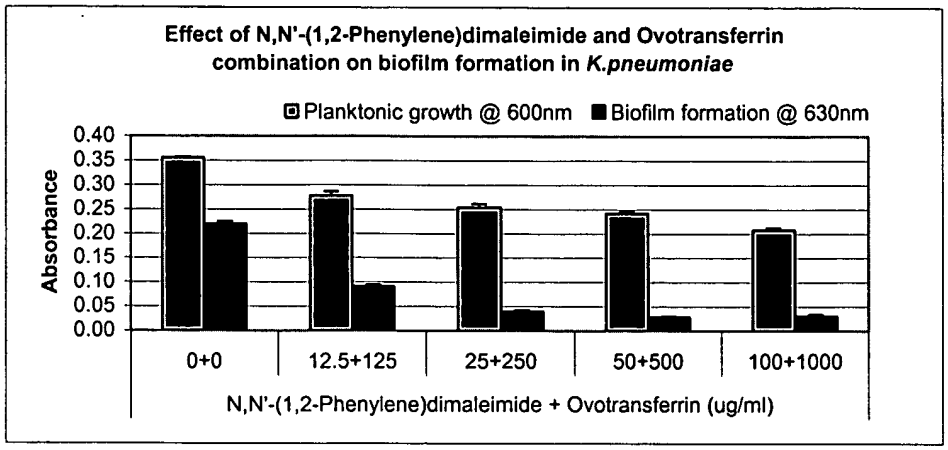

Figure 22: ~~Combined effects of N,N'-(1,2-phenylene) dimaleimide and ovotransferrin on biofilm formation in *P. aeruginosa*~~

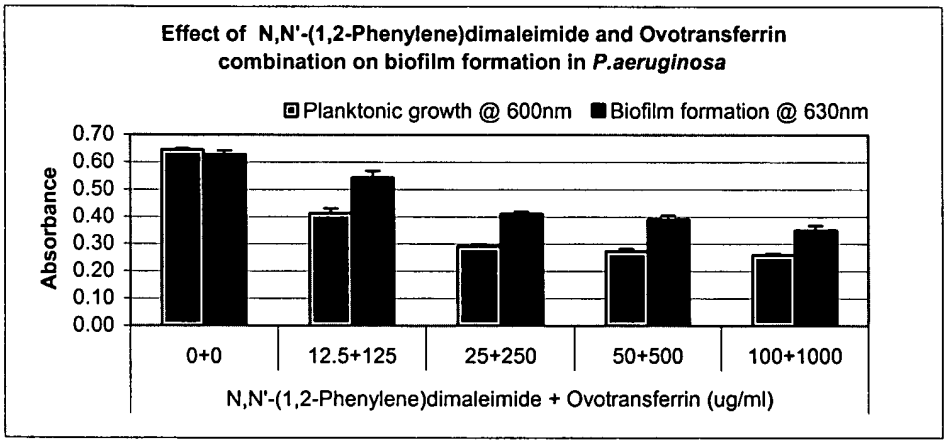

Figure 23: ~~Combined effects of N,N' (1,2 phenylene) dimaleimide and ovotransferrin on biofilm formation in *Enterococcus faecalis*~~

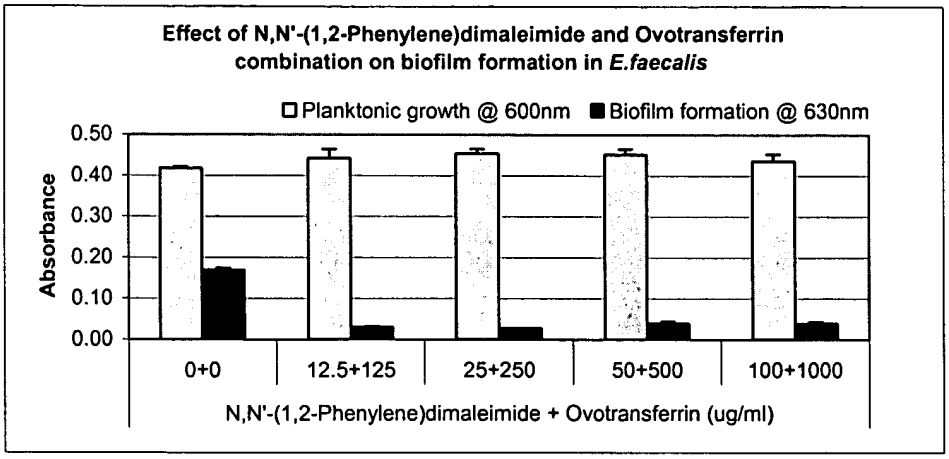

Figure 24: ~~Combined effects of N,N' (1,2 phenylene) dimaleimide and ovotransferrin on biofilm formation in *Staph. Epidermidis*~~

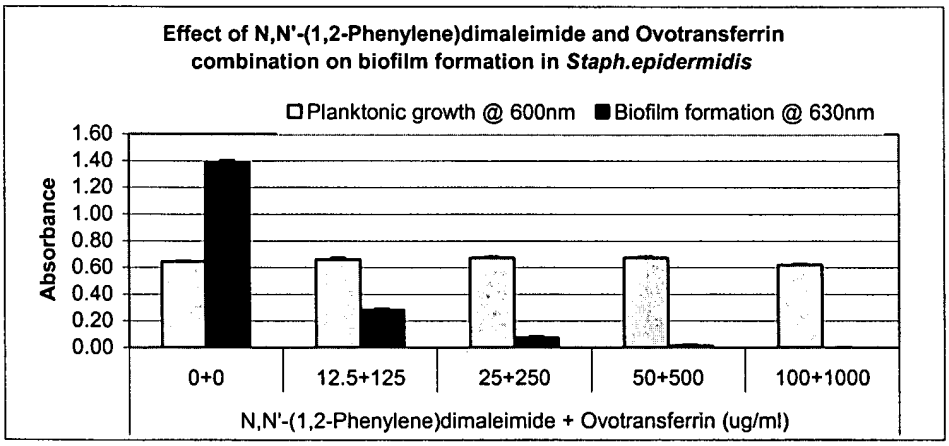

Figure 25: ~~Combined effects of N-(1-pyrenyl)maleimide and protamine sulfate on biofilm formation in *E. coli P18*.~~

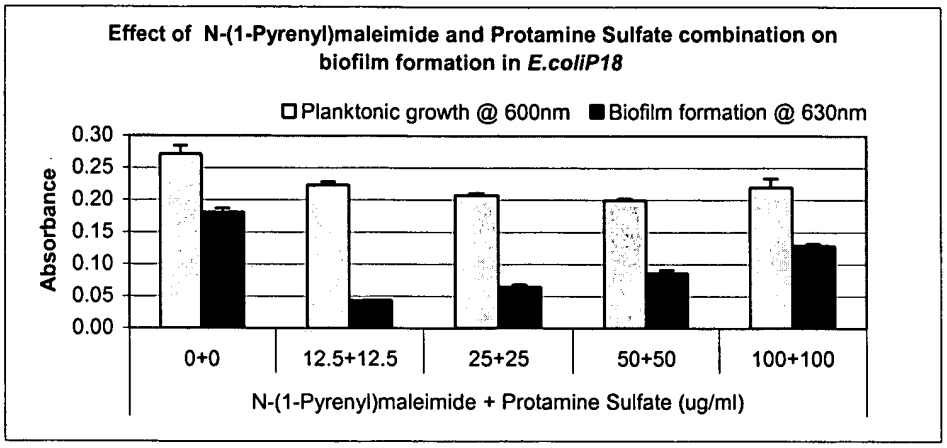

Figure 26: ~~Combined effects of N-(1-pyrenyl)maleimide and protamine sulfate on biofilm formation in *Proteus mirabilis*~~

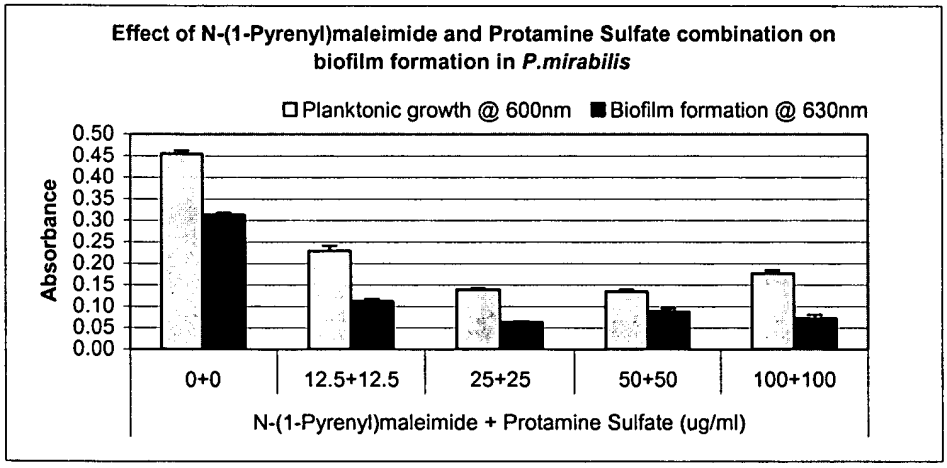

Figure 27~~: Combined effects of N-(1-pyrenyl)maleimide and protamine sulfate on biofilm formation in *Klebsiella pneumoniae*.~~

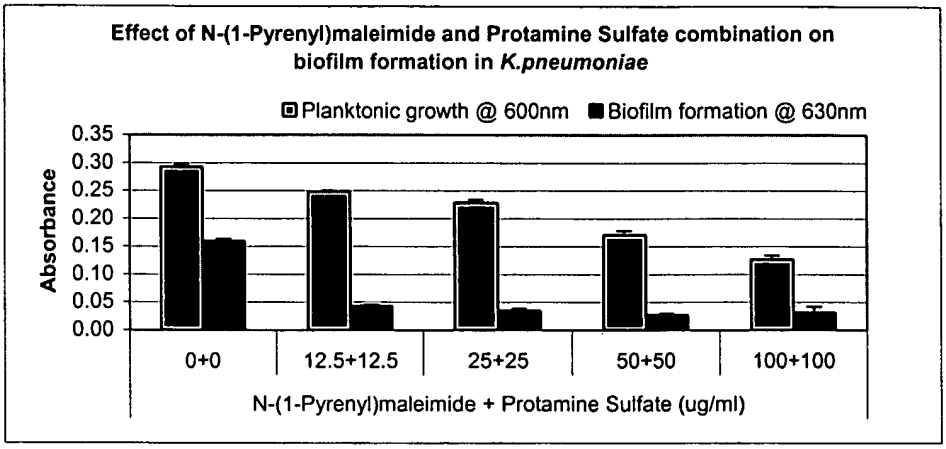

Figure 28~~: Combined effects of N-(1-pyrenyl)maleimide and protamine sulfate on biofilm formation in *Pseudomonas aeruginosa*.~~

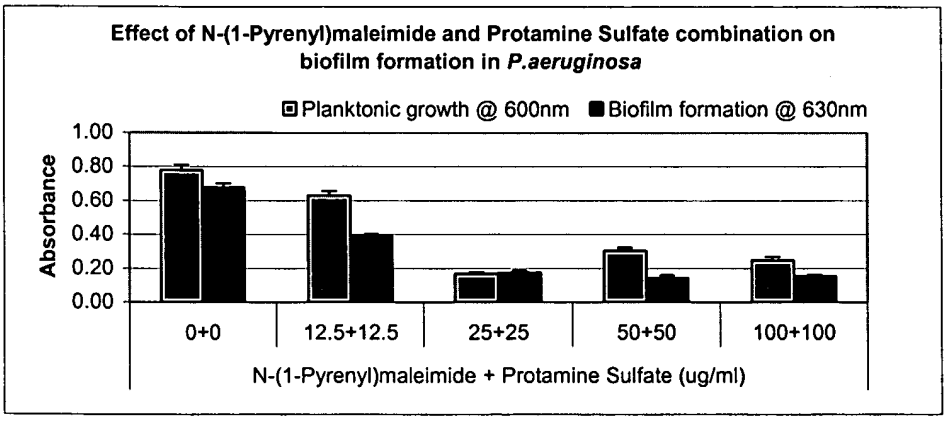

Figure 29~~: Combined effects of N-(1-pyrenyl)maleimide and protamine sulfate on biofilm formation in *Enterococcus faecalis*.~~

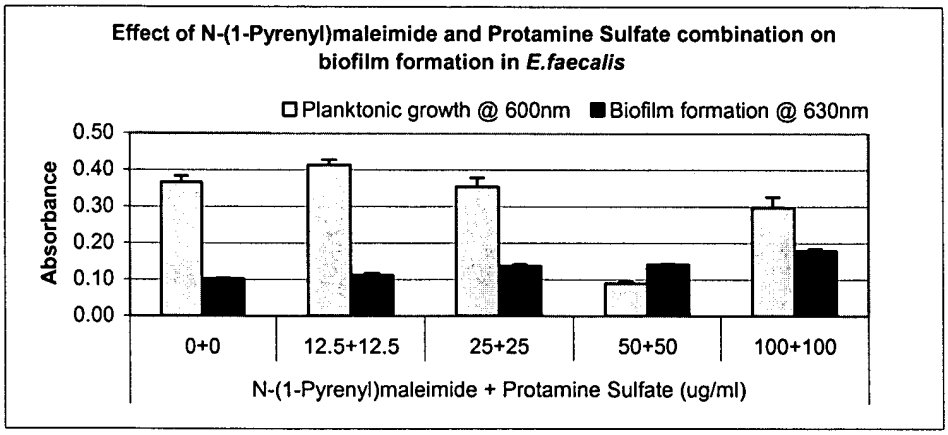

Figure 30~~: Combined effects of N-(1-pyrenyl)maleimide and protamine sulfate on biofilm formation in *Staph. epidermidis*.~~

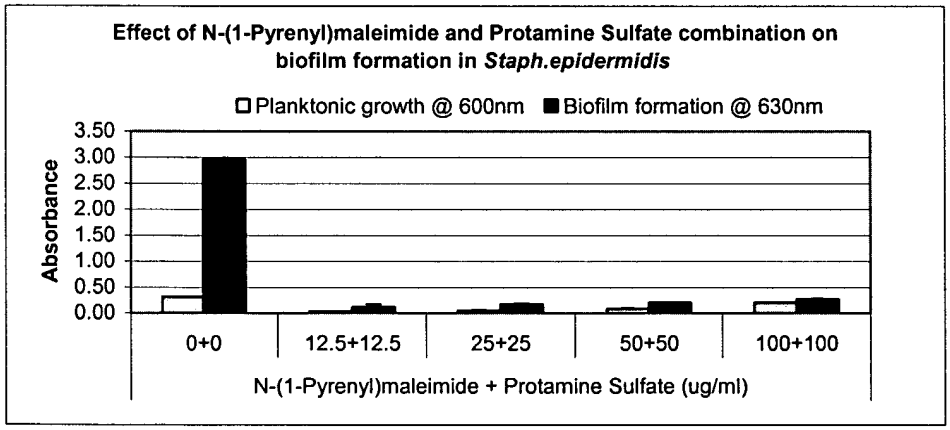

Figure 31: ~~Combined effects of N-(1-pyrenyl)maleimide and ovotransferrin on biofilm formation in *E. coli P18*.~~

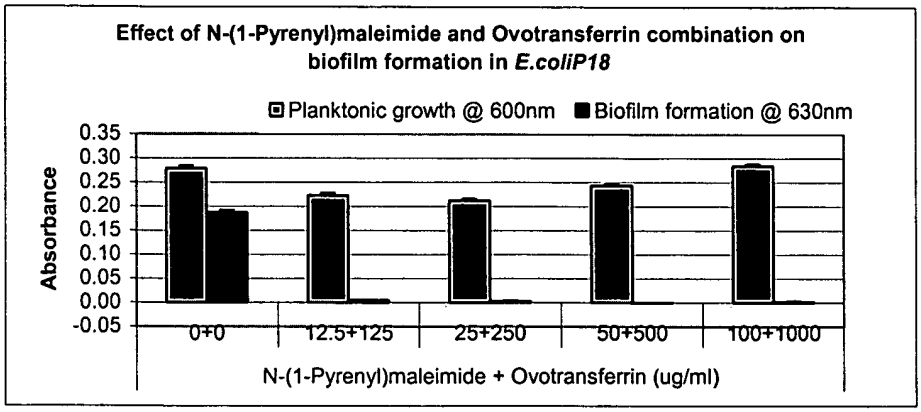

Figure 32: ~~Combined effects of N-(1-pyrenyl) maleimide and protamine sulfate on biofilm formation in *Proteus mirabilis*.~~

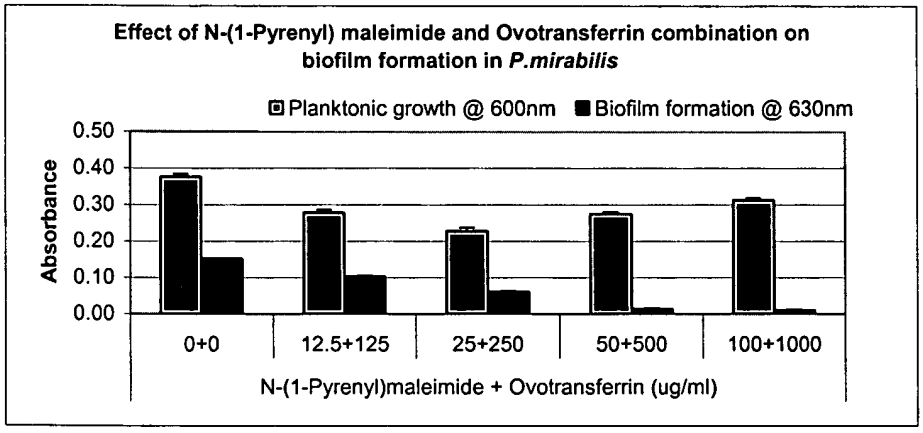

Figure 33~~: Combined effects of N-(1-pyrenyl)maleimide and ovotransferrin on biofilm formation in *Klebsiella pneumoniae*~~

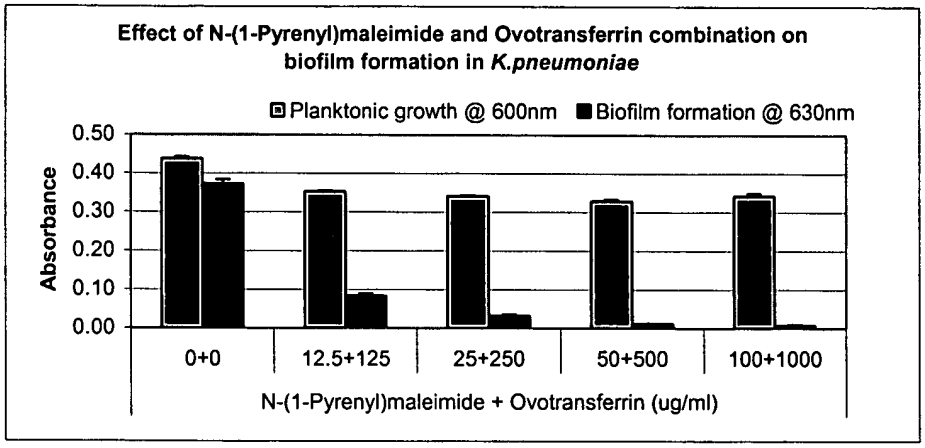

Figure 34~~: Combined effects of N-(1-pyrenyl)maleimide and ovotransferrin on biofilm formation in *Pseudomonas aeruginosa.*~~

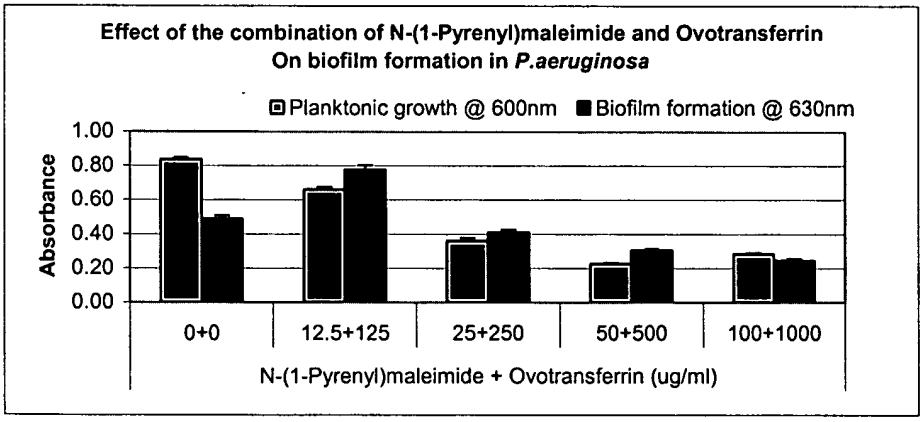

Figure 35~~: Combined effects of N-(1-pyrenyl)maleimide and ovotransferrin on biofilm formation in *Enterococcus faecalis*.~~

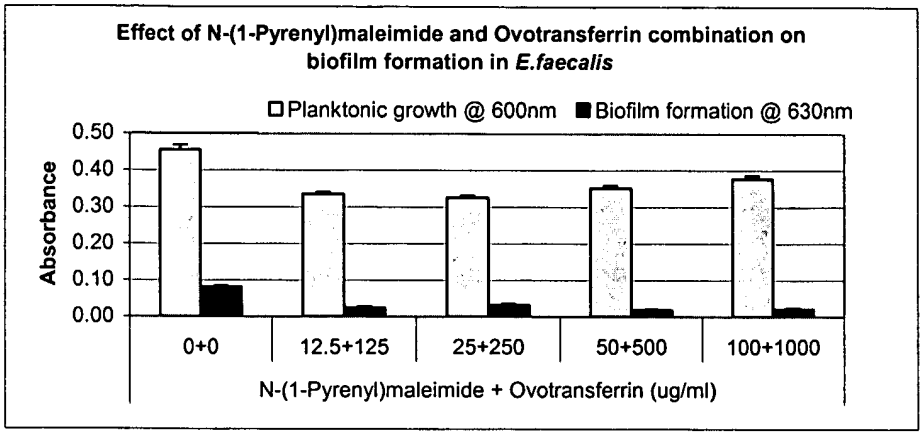

Figure 36~~: Combined effects of N-(1-pyrenyl)maleimide and ovotransferrin on biofilm formation in *Staph. Epidermidis*~~